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ABSTRACT

This report is comprised of three separate studies conducted at the University of Colorado Medical Center. In the first study, answers to the following questions were sought: (1) What kinds of late morbidity occur at different birth weights and gestational ages? and (2) Has a vigorous approach to metabolic support in the newborn period changed the outcome of the low-birth-weight infants? In the second study, complications resulting from the use of indwelling umbilical vein catheters in newborn infants was studied when the infants were from 9 months to 2 years of age. In the third study, head shape and size of normal newborn infants were studied in their relationship to gestational age and birth weight. Results of the studies are discussed and tabulated. (Seven figures in the original document are not included because of nonreproducibility.)
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High-Risk Follow-Up Study - HEW - H-224

Part I

THE LONG-TERM OUTCOME OF CHILDREN
BY BIRTH WEIGHT AND GESTATIONAL AGE

INTRODUCTION

The outcome of infants of very low birth weight is known to be poor. The incidence of central nervous system (CNS) damage is high and manifested mainly by intellectual retardation and spastic diplegia. Data on outcome related to gestational age and intrauterine growth is meager and specific morbidities related to gestational age have not been well defined.

Previous studies from this Center have shown a relationship of outcome between birth weight and gestational age in very small infants. If only children with moderate and severe handicaps are considered afflicted, the incidence was 85% in survivors with birth weights <1000 grams and with a gestational age of <28 weeks. The percentage of handicapped children decreased at this gestational age as birth weight increased toward 1500 grams and improvement in outcome occurred at the same birth weight, when gestational age was prolonged. The best prognosis, 20%, occurred at 1350-1500 grams, with a gestational age of 32-34 weeks.

The incidence of handicapped children at various birth weights over 1500 grams, at different gestational ages, has been reported by Drillien in a retrospective study of her data on low birth weight and current data by birth weight and gestational age are still being accumulated.

Weiner also reviewed data on I.Q. by birth weight and gestational age of children followed at approximately 8 years of age and found a surprisingly high handicap in intelligence in children with birth weights >2500 grams, if their gestational ages were less than 38 weeks.

Data on neonatal findings and problems in term, small-for-gestational-age (SGA) infants versus pre-term, appropriate-for-gestational-age (AGA) infants has been reviewed by North, Yerushalmy and others. The term SGA infant is more likely to have congenital anomalies (North, Yerushalmy) and to become hypoglycemic in the immediate postnatal period (Cornblath, Neligan, Lubchenco and Bard).

The outcome of infants with symptomatic neonatal hypoglycemia is poor, but the cause and effect of low blood sugar on CNS development is not at all certain.

Another curious finding in follow-up studies of low-birth-weight infants is an apparent fluctuation in the incidence of handicaps from year to year and from center to center. For example, Hess, Gessel, Shirley and others recognized the increased risk of handicap, but believed the number of such involved children to be small and the severity of handicaps to be mild. The data of Hess are particularly impressive in the

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completeness of the survey and the care and critique with which the examinations were done.

Reports from the 1950's are in contrast to these earlier data. Since 1955, an increasing number of reports concerning former pre-term infants show them to be abnormal. Dann, et al, found a lowering of the I.Q. in 44% of the children whom they were able to follow, but very few physical defects. Drillien reported intellectual, behavioral and physical defects in more than 60% of her series. Data from this Center are in agreement with Drillien's.

Drillien further showed a lowering of I.Q. in patients subjected to a prolonged period of starvation following birth. This finding has given impetus to the possible relationship of postnatal practices and later outcome. It is well-known that certain routines have been responsible for a poor prognosis, such as oxygen therapy and retrolental fibroplasia or Gantrisin and the development of kernicterus. The question, at present, is whether or not there are postnatal practices which will improve the outlook for normal growth and development.

Reports in the past year or two are beginning to indicate an improved prognosis with intensive newborn care. Stahlman showed a remarkably good outcome in infants with respiratory distress syndrome (RDS)--treated vigorously to maintain biochemical homeostasis--and Rawlings, et al, have presented the most optimistic figures to date on mortality, morbidity and later outcome of very low-birth-weight infants.

There is some difficulty in comparing follow-up studies because of the differing populations selected and because of a lack of a standard for normality. It is imperative to examine the criteria set down for severity of defect before comparisons with other data can be made with certainty. For instance, Rawlings considers a patient with an I.Q. of over 80 a normal child; whereas, in the present data, an I.Q. of 90-110 is considered normal.

The present study was undertaken to answer the following questions: (1) What kinds of late morbidity occur at different birth weights and gestational ages? (2) Has a vigorous approach to metabolic support in the newborn period changed the outcome of low-birth-weight infants?

CLINICAL MATERIAL AND METHODS

All surviving children from a 2-year period, 1963-1965, and born at the University of Colorado Medical Center, constituted the sample to be followed at approximately 4 years of age. They were grouped by 500-gram birth weights and 2-week gestational ages into blocks of cases from which all, or random samples, would be chosen to be returned for evaluation.

In Figure 1 can be seen the distribution by birth weight and gestational age of all births and survivors, while in Figure 2 the blocks from which all survivors were to be examined are identified.

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Infants with birth weights of 1500 grams or less constituted a group of infants who were similar to samples previously studied and would be expected to show the effects, if any, of intensive metabolic support during the neonatal period.

The other 4 blocks delineate the pre-term AGA infants from similar weight, but term SGA infants. All survivors in these 5 blocks were chosen for review.

In order to obtain a comprehensive view of the incidence of handicaps in the total newborn population, a random sample of 5 children from each birth weight-gestational age block was chosen for review. As the study progressed it became apparent that there was not a smooth trend in the incidence of handicap, starting with the highest incidence in the smallest infants of shortest gestational age to a low point in the term AGA infants. Therefore, the sample was enlarged especially in the blocks adjacent to the pre-term AGA samples where the discrepancy occurred and, in addition, children from a previous year, with birth weights 1500-2000 grams, were added to the sample.

The children from the 5 target blocks received detailed examinations, including a medical history and physical examination, neurologic examination, encephalogram, psychometric testing, ophthalmological examination, audiometric testing, speech evaluation and review of social situation. The children outside of the target blocks received the same detailed medical history and physical examination, but only screening tests for vision and hearing were done. The Denver Developmental Screening Test, the neurological and ophthalmological examinations were done by the chief investigator and clinical fellow. Psychometric testing was added after the study was underway.

Information from the examinations was transcribed from special follow-up study forms to code sheets and thence to computer tapes for further study and correlations.

Data from the hospital records of children who expired, or who survived but were not seen, were also coded for the 5 target blocks.

The severity of handicaps found in the patients studied was graded from 0 to 4+, and the items used to determine the severity are listed in Table I.

RESULTS

The total number of patients followed was 350. This number included 1 sibling of a patient in the study and 6 on whom incomplete information was obtained from clinic follow-up visits; leaving 343 children on whom data were available for analysis of outcome by birth weight and gestational age.

Data from an additional 79 charts were coded to complete the information on all admissions to the 5 target blocks, 43 of the 79 patients

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expired during the neonatal period and no follow-up information was available on 36 children.

In Figure 3, the number of coded charts in each birth weight-gestational age block is listed and in Figure 4 is the distribution of the 343 children on whom the analyses were made.

The incidence of handicaps by birth weight and gestational age in the 343 children followed is shown in Figure 5. In this chart, all handicaps are included, i.e., congenital anomalies, as well as multiple minor conditions which add up to plus 1 or 2 handicaps, as listed in Table I.

Table I

DEFINITION OF HANDICAPS

Degree of Handicap	Type of Handicap
0	IQ 90 or more Emotional problems, mild/moderate Febrile convulsions Abnormal EEG Myopia or other refractive error Conduction hearing loss Speech problem, mild/moderate Strabismus
1+	IQ 80 to 89 Mild cerebral palsy Minimal cerebral dysfunction Perceptual motor problem Congenital heart disease Cleft palate/harelip Mild neurosensory hearing loss Severe emotional problem Severe speech problem Congenital defect, spine 3 or more "0" conditions (see above)
2+	IQ 70 to 79 Moderate neurosensory hearing loss Definite neurologic abnormality Non-febrile convulsions Hydrocephalus 2 or more "1+" conditions (see above)
3+	IQ <70 Severe neurologic abnormality Severe hearing loss
4+	Expired

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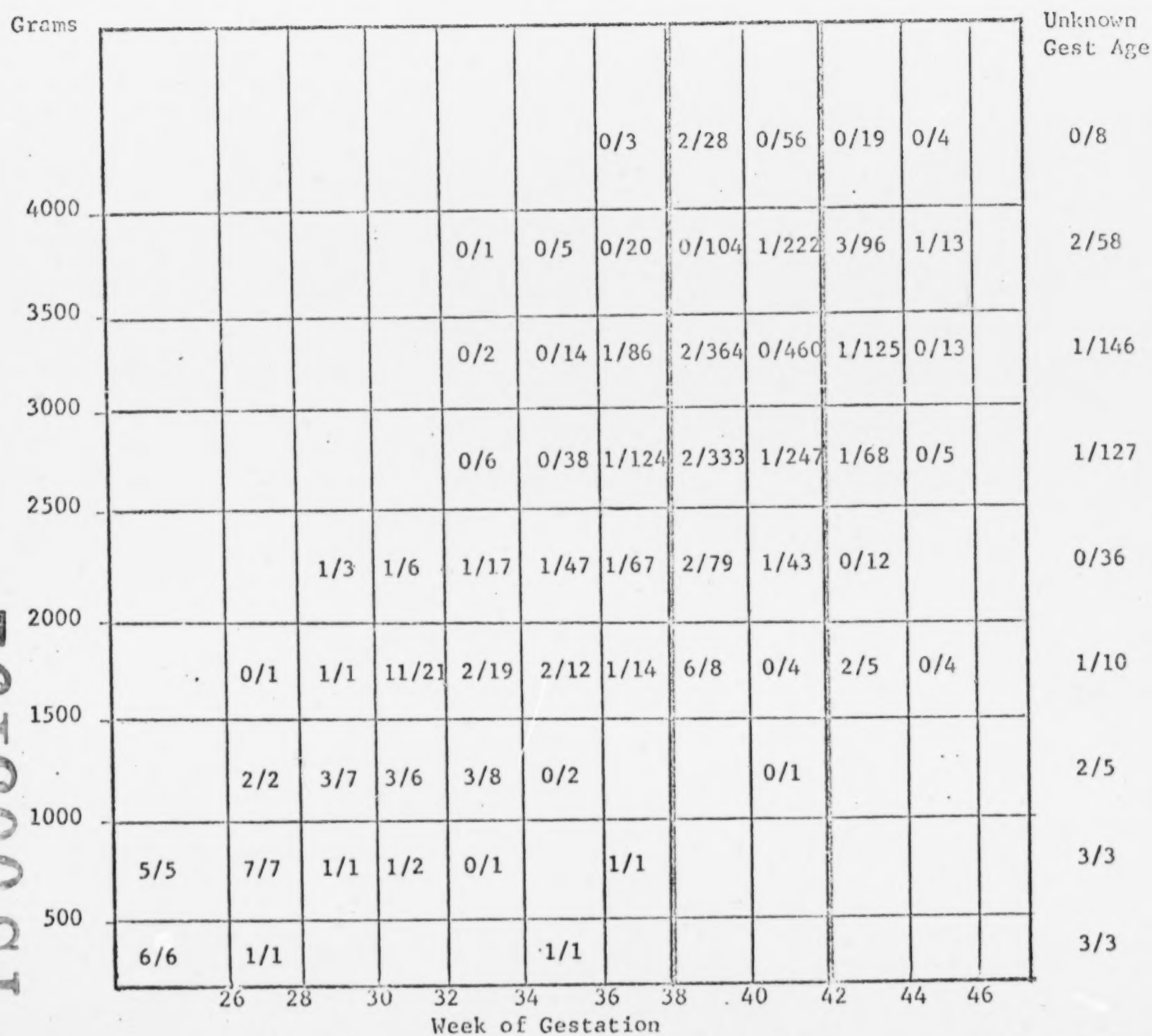
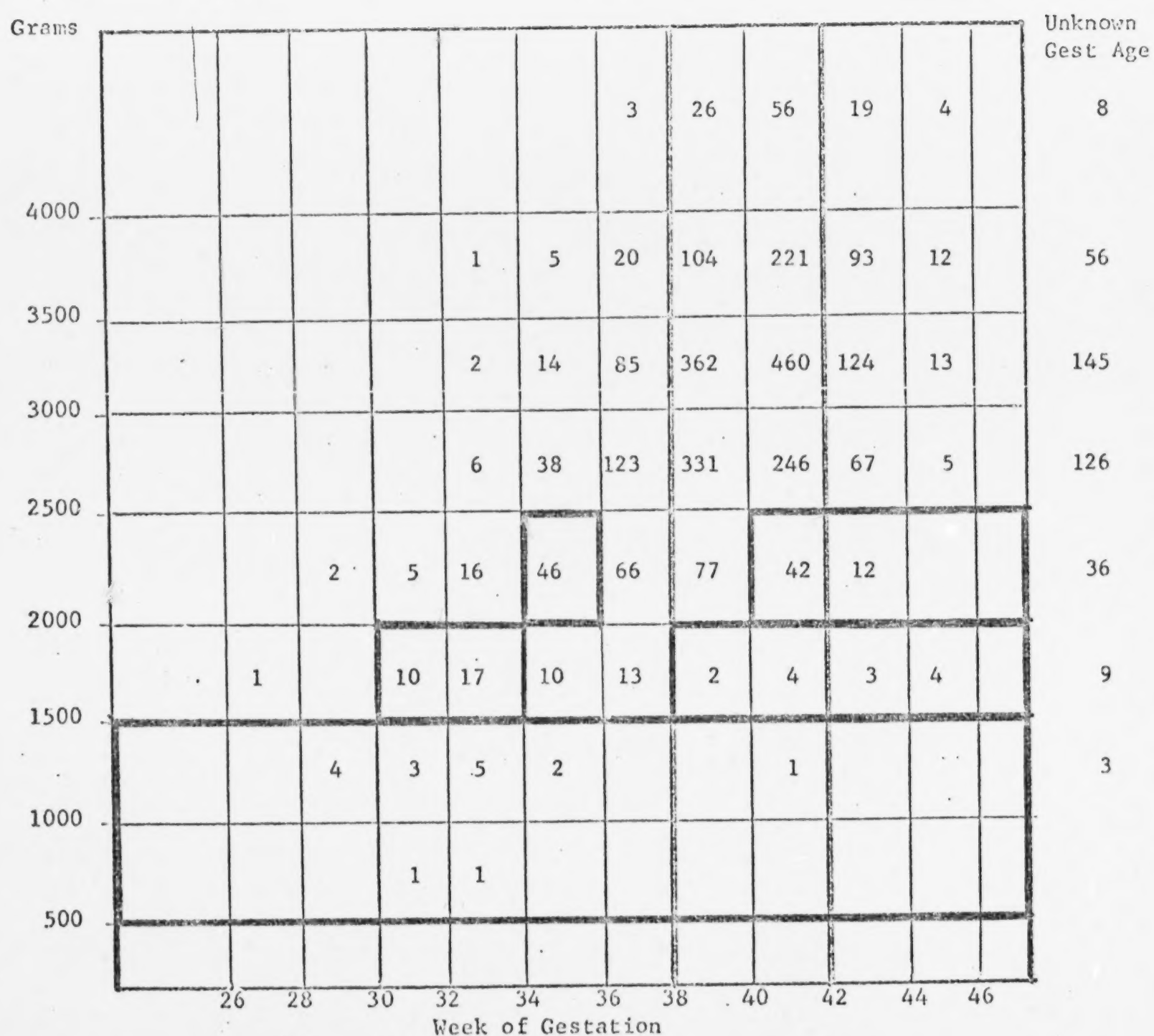


Figure 1. Neonatal mortality by birth weight-gestational age groups. UCMC newborn admissions, 1 July 1963 - 1 July 1965.



Grams	26	28	30	32	34	36	38	40	42	44	46
4500								2	3		
4000						1	6	3	2	3	
3500				1	3	5	7	7	4	3	
3000				1	4	4	13	9	6	5	
2500				4	17	26	14	11	5	2	
2000			1	2	9	46	29	10	29	7	1
1500		1	2	12	26	8	7	9	3	4	2
1000	1	2	6	5	8	1	1		1		
500	7	7	3	2	2		1				

Figure 3. Distribution by birth weight and gestational age. Coded data from 426 patients.

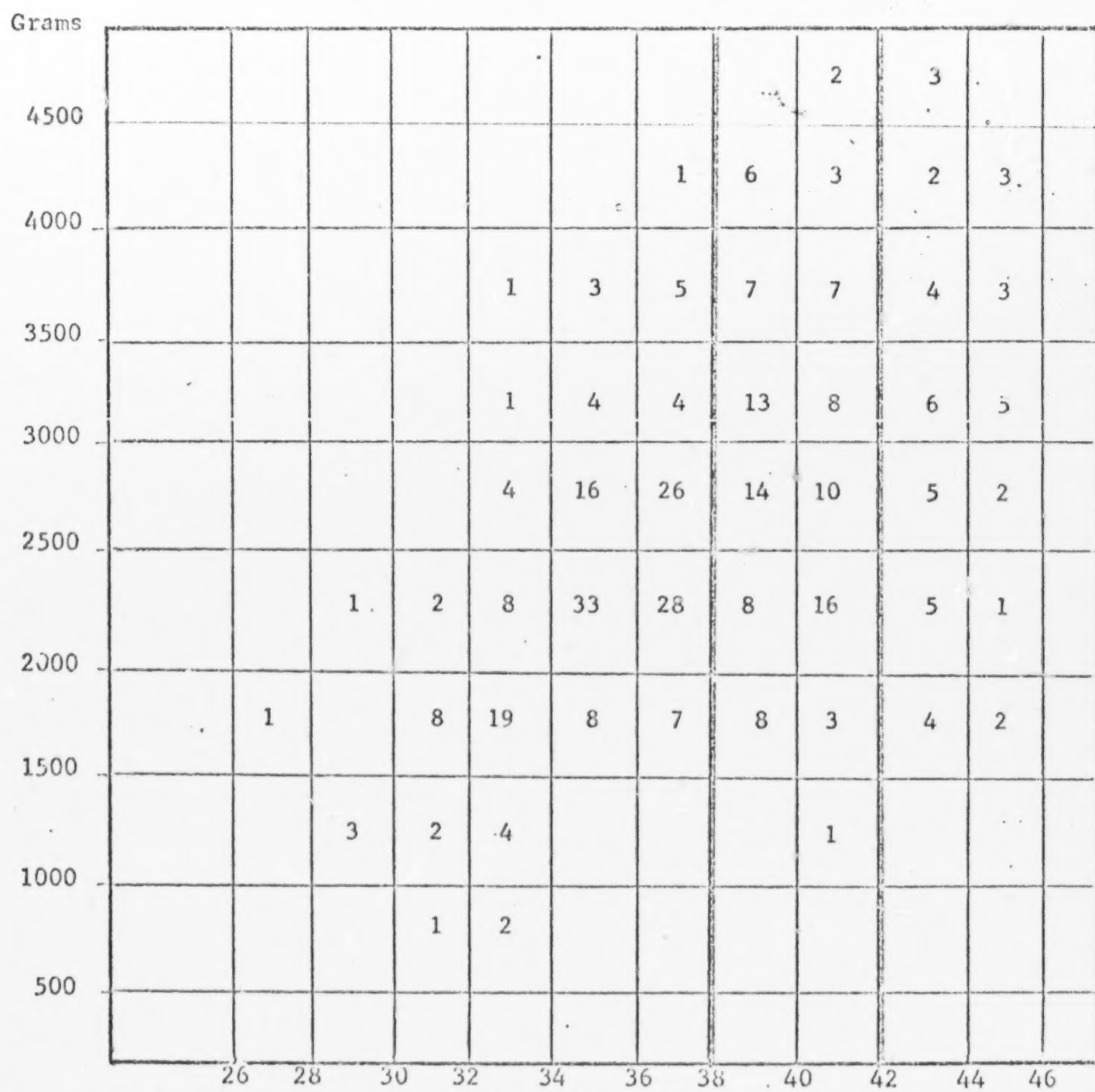


Figure 4. Distribution of 343 patients; follow-up data used for analysis.

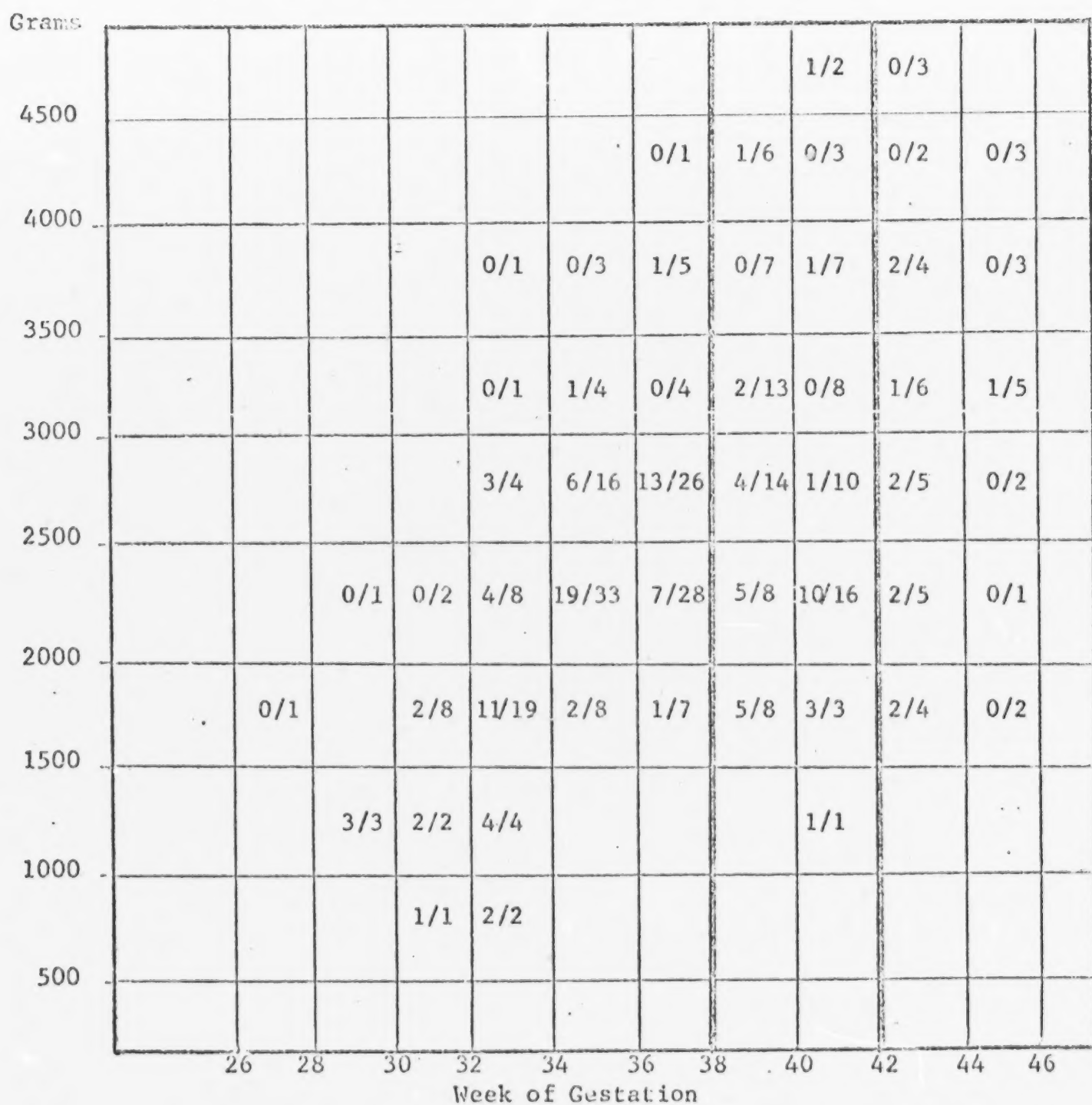


Figure 5. Incidence of handicaps in 343 children followed (anomalies and minor handicaps included).

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The unevenness related to small numbers is apparent, as is the very high incidence of handicapped children seen in this study. When the data are grouped into larger blocks, the result can be seen in Figure 6.

Because of the high incidence of handicaps noted previously, it was decided to examine the incidence of problems when congenital anomalies and minor conditions were removed. In Figure 7 are 1+ handicaps, based on an I.Q. of 80-90, spastic diplegia and definite minimal cerebral dysfunction. Anomalies, which were related to the handicap, were removed; while children with congenital heart disease, club feet, and other non-handicapping anomalies remained in the study.

The incidence of handicaps in the target blocks can be seen in Figure 8.

The I.Q. by birth weight and gestational age was also examined and can be seen in Figure 9. When no psychometric examination was available, the clinical estimate--based on the Denver Developmental Screening Test, developmental landmarks and clinical impression of the investigators--was used. This impression was expressed as a 10-point range and the mid-point in the range was used as the I.Q.

In Figure 9, mean I.Q. is shown by each birth weight-gestational age block, and in Figure 10, the mean I.Q. in the target blocks is seen.

The 1500- to 2000-gram AGA group stands out as improved over the 2000- to 2500-gram AGA group.

A distribution of I.Q.'s in these 2 groups was made (Figure 11). The 2000- to 2500-gram infants have a relative shift of I.Q.'s toward the left, i.e., 80-90, and there is a suggestion of a bimodal curve.

A closer look at the target samples of pre-term AGA infants without handicapping anomalies reveals the following:

Infants with birth weights <1500 grams did not fare well. There were 2 with normal I.Q.'s (>90) and 4 with I.Q.'s between 80 and 90. All 6 were over 1000 grams at birth; 5 had no CNS defect and the 6th had only suggestive signs of spastic diplegia. Six out of 7 relatively normal children with birth weights between 1000-1500 grams could be cause for optimism except that the long-term, educational outlook for persons with I.Q.'s in the 80-90 range is not favorable. Nine of the 10 had obstetric, labor and/or delivery complications. All 10 were cared for in the Intensive Care Nursery. Eight of the 10 received IV fluids, 6 of the 10 had respiratory distress and 6 had apneic periods; for a total of 8 with one and/or the other. The child with the highest I.Q. had no obstetric or delivery problems, had a good 5-minute Apgar, no resuscitation was needed, but he had severe respiratory distress and apneic periods. Oral feedings were begun at 9 hours, but IV therapy was instituted at 14 hours.

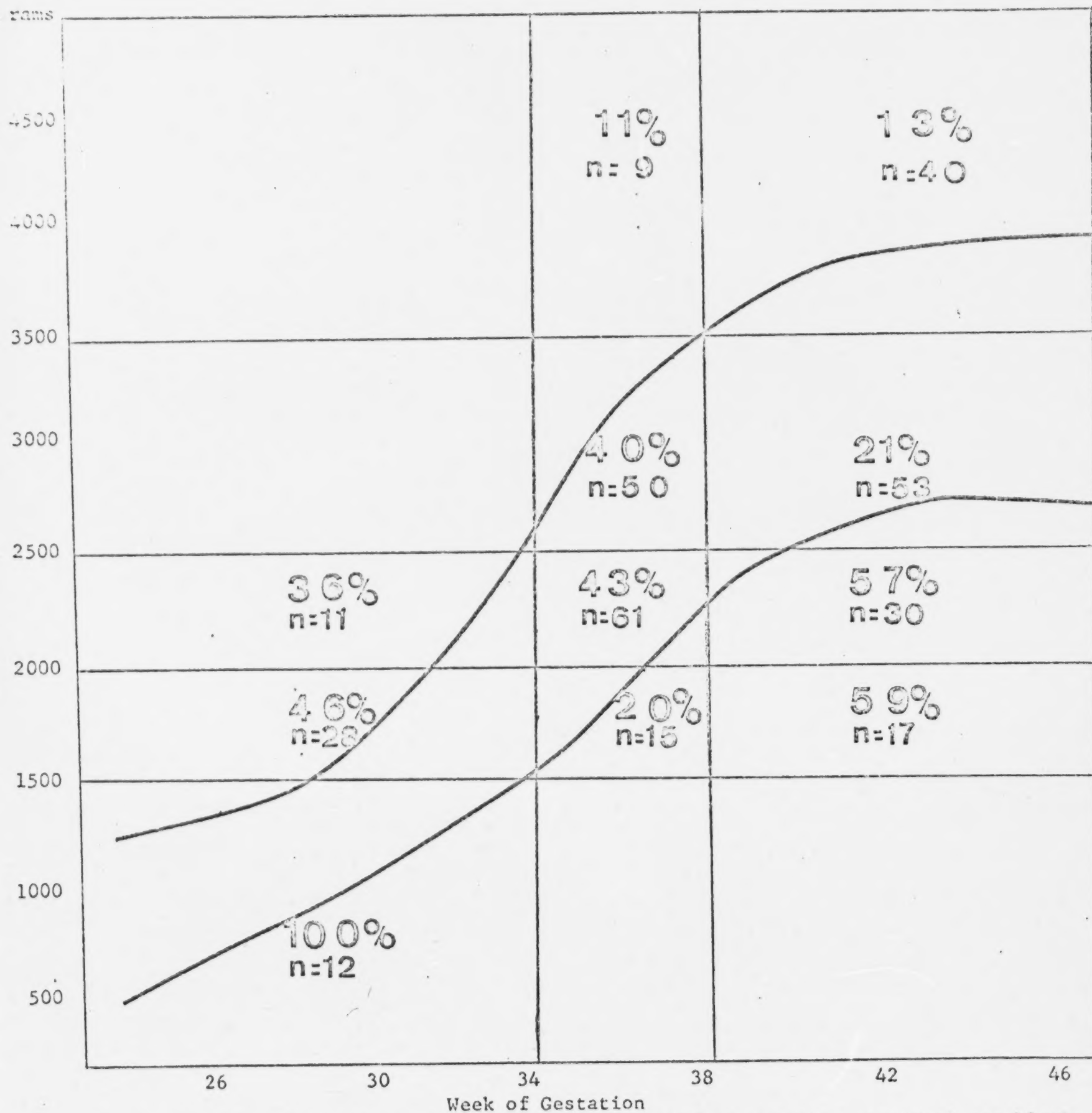


Figure 6. Overall incidence of handicaps by large birth weight-gestational age blocks. Congenital anomalies and minor handicaps included.

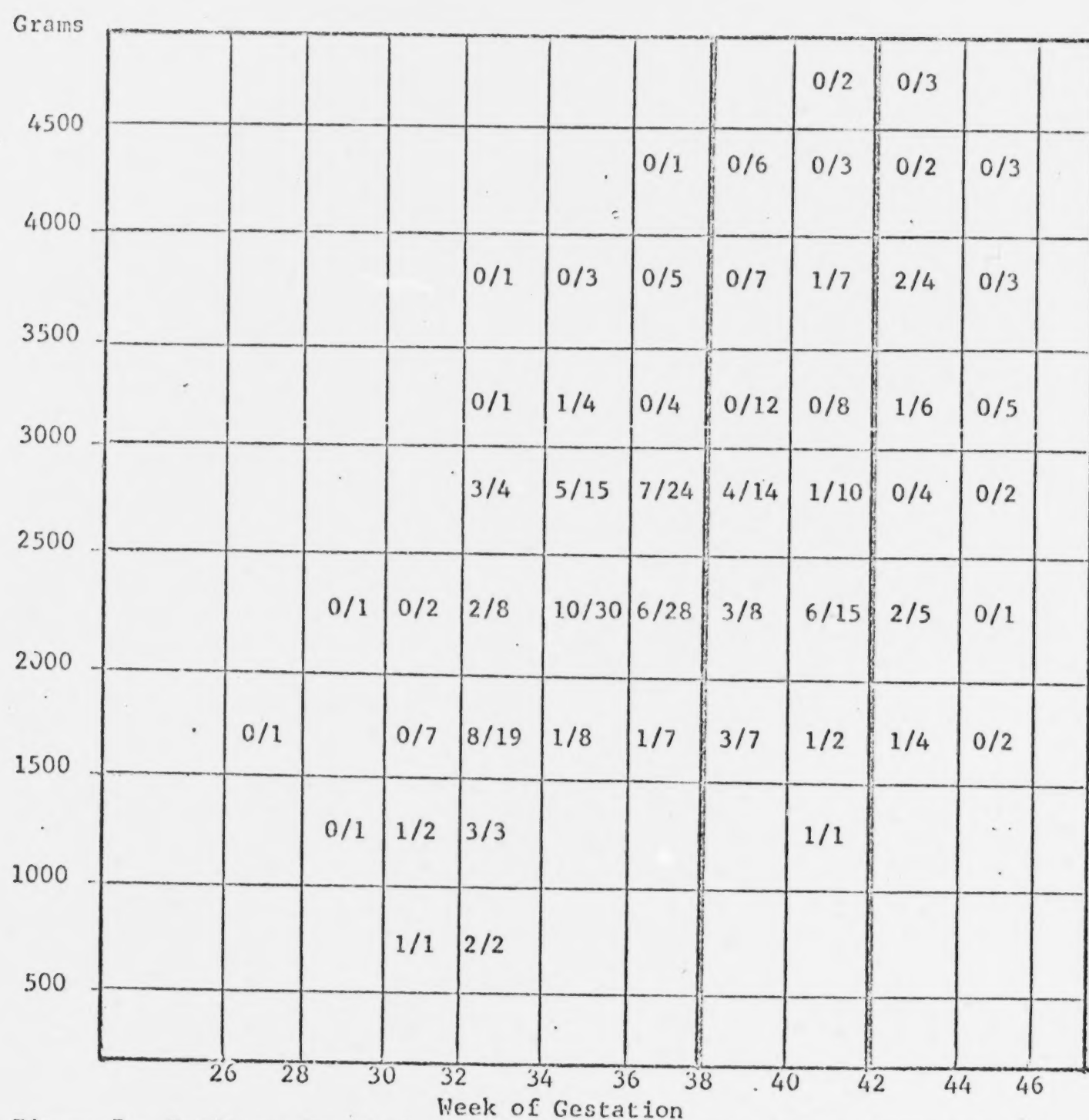


Figure 7. Handicaps by birth weight-gestational age groups (anomalies and 1+ and 2+ handicaps excluded).

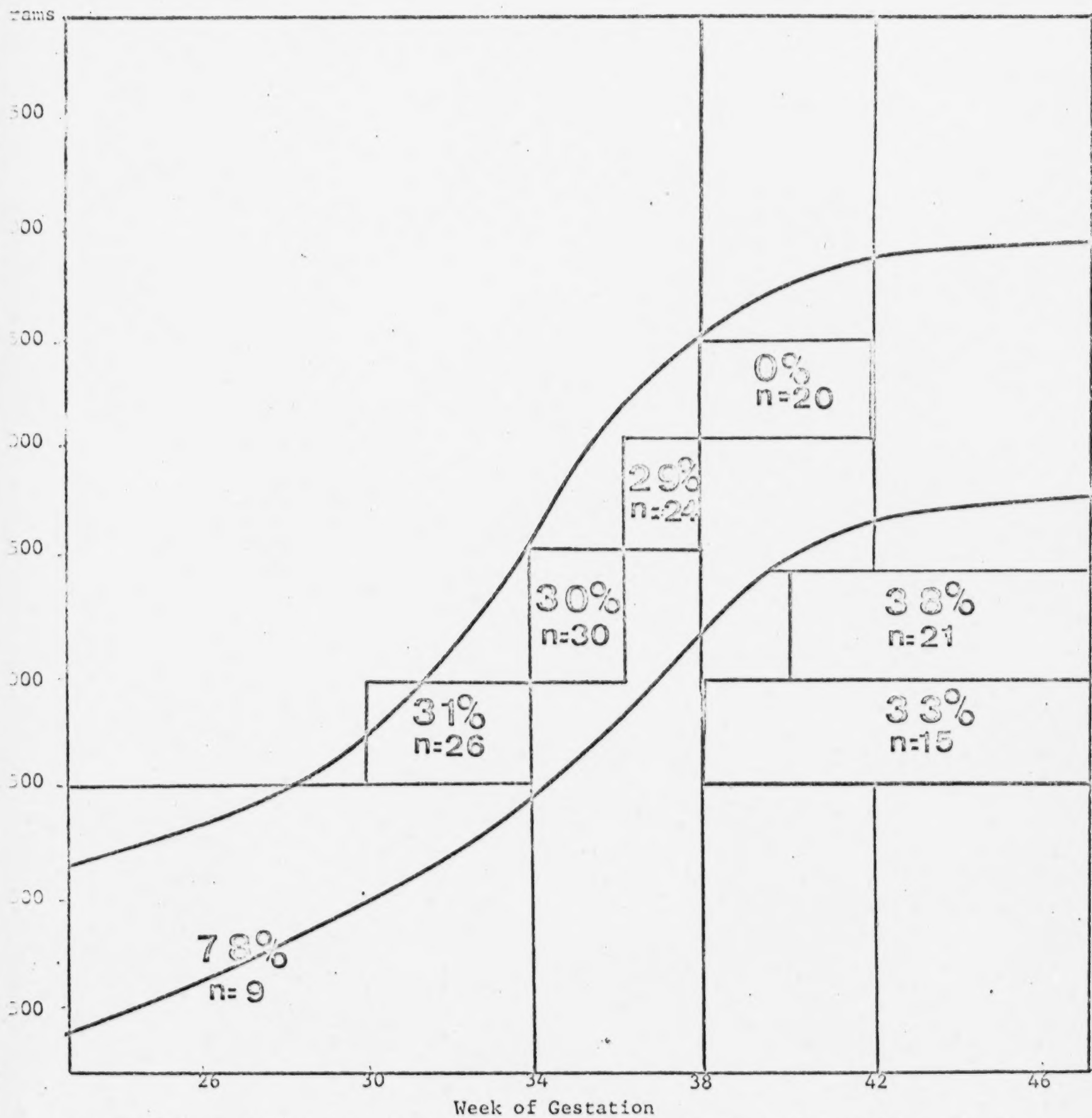


Figure 8. Incidence of handicaps in target blocks. Congenital anomalies and minor handicaps removed.

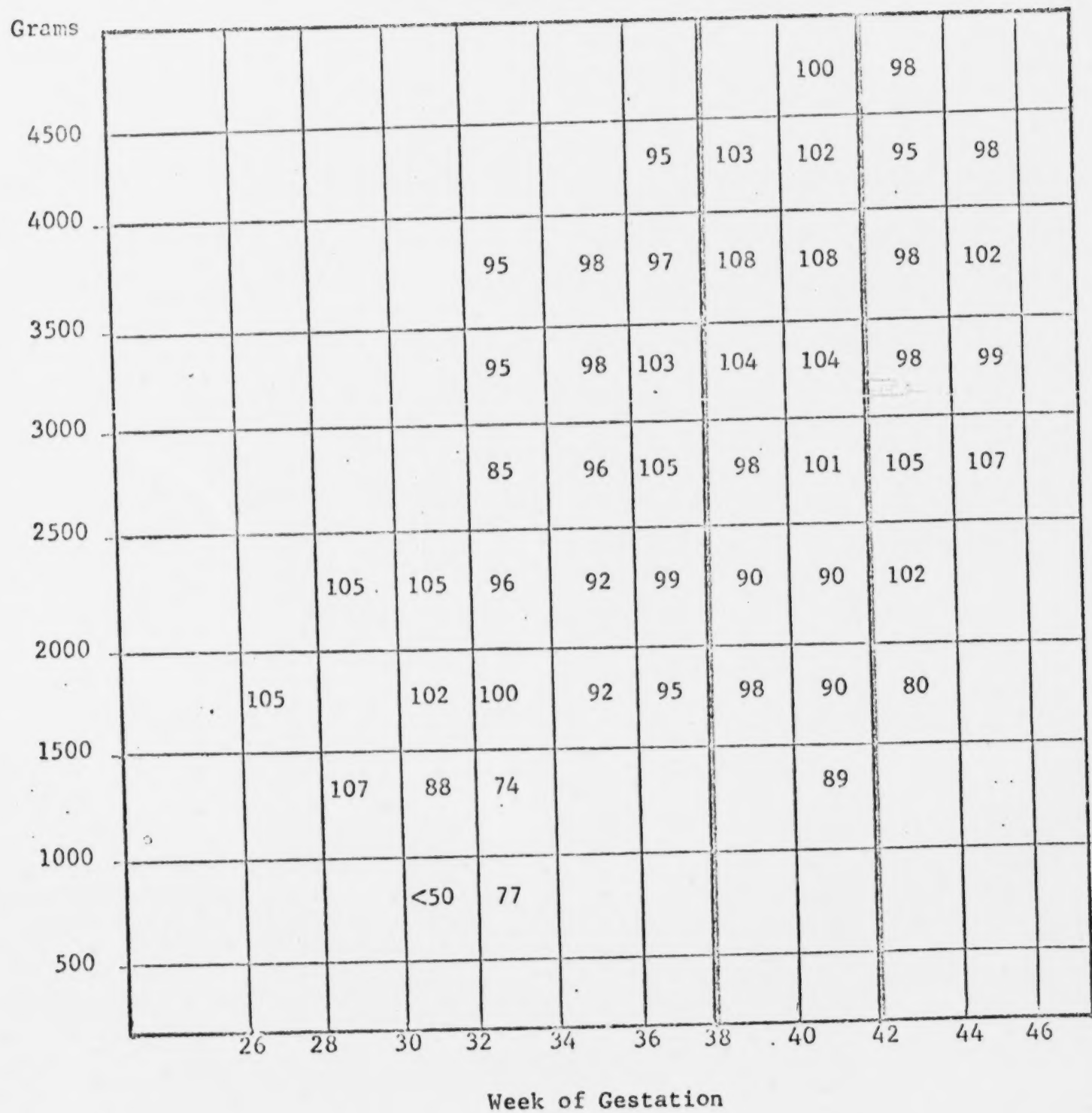


Figure 9. IQ of 318 children without anomalies.

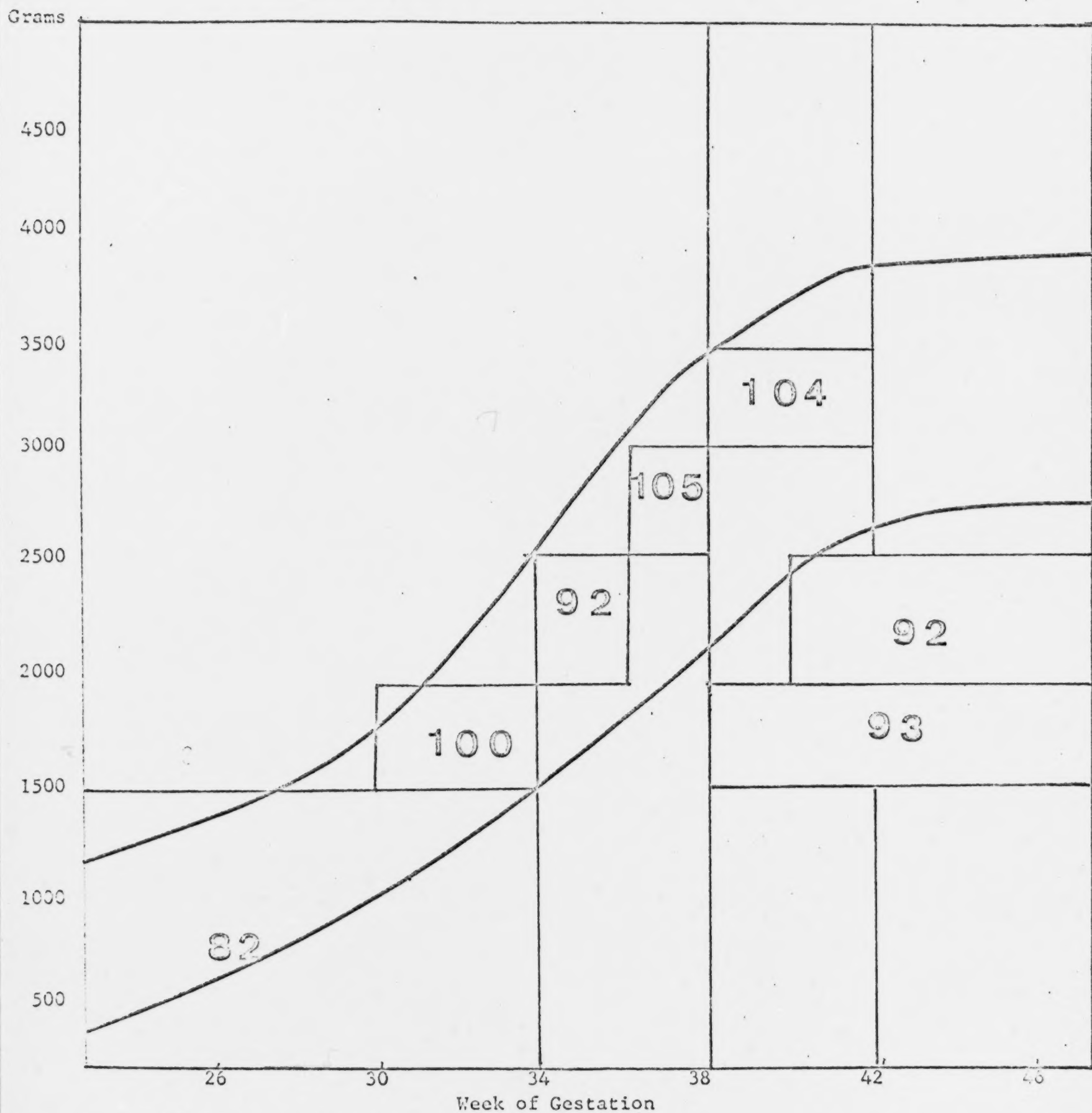


Figure 10. IQ by birth weight and gestational age

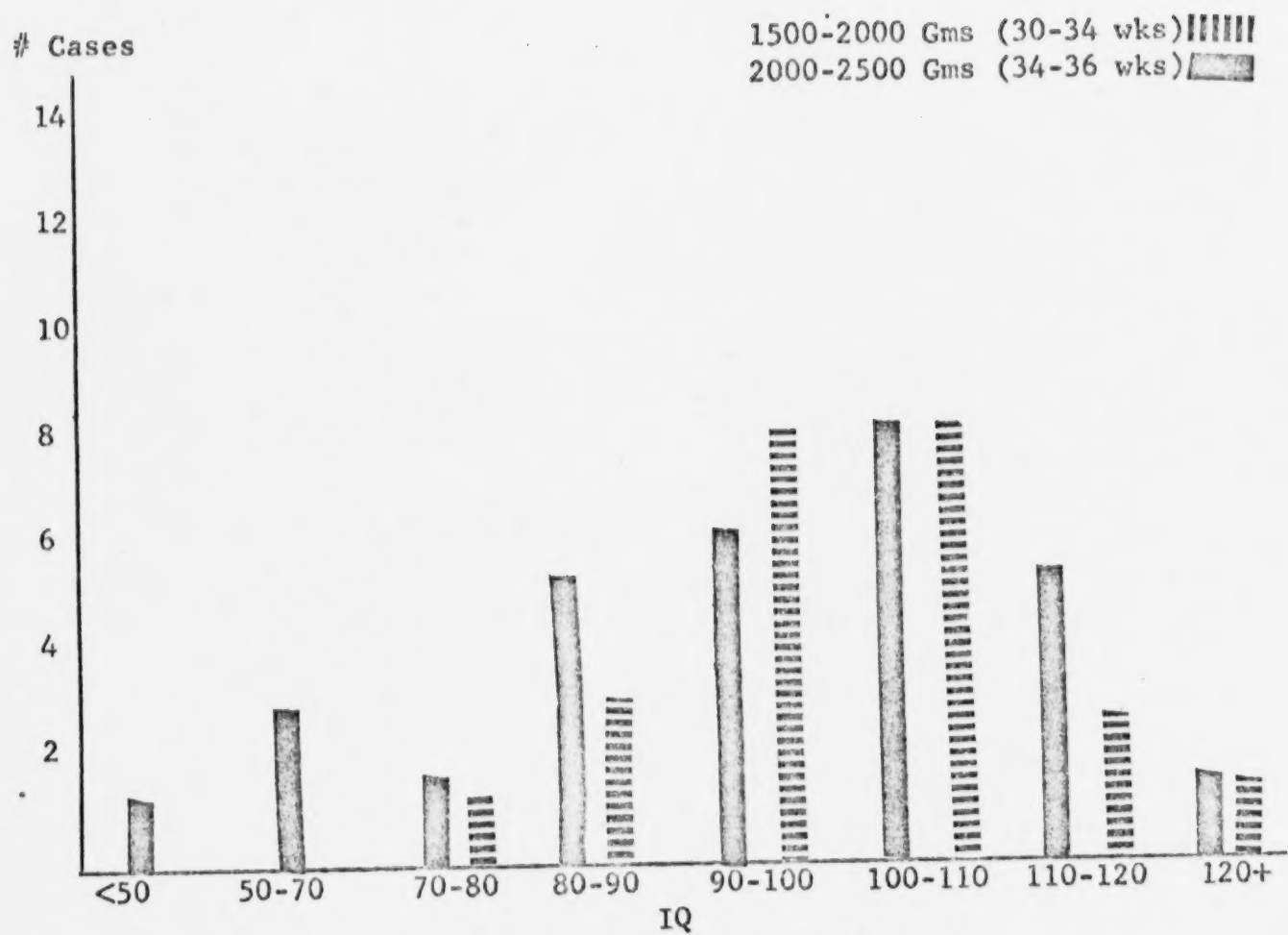


Figure 11. Distribution of IQ by birth weight-gestational groups.

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There was one term SGA infant in the group with a birth weight of <1500 grams. This infant was not given IV fluids, received oral feedings at 21 hours, had no neonatal complications and has an I.Q. of 89.

In the other 2 AGA groups where the smaller, 1500- to 2000-gram, more immature infants had a better outlook than the 2000- to 2500-gram weight group of 34-36 weeks gestation, the following comparisons were made:

I.Q. was the easiest comparison to make and the mean I.Q. of 100 versus 92 is indicative of a difference in the 2 groups ($p = <.10$).

There were 22 out of 26 with I.Q.'s above 90 in the smaller birth weight youngsters and 3 with I.Q.'s between 80-90; leaving only 1 with an I.Q. of 70.

In the larger birth weight group, 17 out of 30 had I.Q.'s above 90 and 3 others were considered normal in clinic follow-up (20/30), 5 were between 80-90 and 5 were grossly retarded.

Except for I.Q.'s, the decision as to severity of handicap was most difficult. CNS signs of spastic diplegia and evidence of minimal cerebral dysfunction presented the greatest difficulty in labeling the children handicapped.

In the smaller birth weight group, there were 5 which presented some CNS signs and 4 of these were considered severe enough to label 1+ handicapped.

In the larger birth weight group, there were 7 presenting CNS signs: none of whom were given a handicap score. Nine out of 26 (35%) were handicapped on the basis of I.Q. and/or CNS signs in the smaller birth weight group and 10 out of 30 (33%) in the larger birth weight group. This percentage could easily change if minimal CNS signs were considered significant.

10/26 versus 17/30 or 38% versus 57%

Table II

MATERNAL AND NEONATAL COURSE

Smaller Birth Weight AGA Infants		Larger Birth Weight AGA Infants	
Obstetric and/or delivery complication	22/26		18/30
Low 1-minute Apgar	18/26		9/30
Low 5-minute Apgar	3/26		2/30
Resuscitation needed	10/26		3/30
RDS	15/26		2/30
Apnea	5/26		1/30
IV therapy	14/26		1/30
Intensive Care Nursery	24/26		10/30

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The two groups were then combined and reorganized according to postnatal treatment. Since intensive care seemed to be a prominent factor in the smaller birth weight group and since 1/3 of the larger birth weight infants received this type of care, the outcome of the children was related to whether or not they received intensive care.

Table III

NURSERY CARE

	Intensive Care	Regular Care
# of infants	34	22
# with RDS	15	2
# receiving IV fluids	15	0
# I.Q. >90	29	13
Mean I.Q.	97	94
# minimal and definite CNS findings	9	6
# abnormal I.Q. and CNS	10/34	9/22
(including minimal findings)	13/34	14/22

A closer look at the type of treatment given in the Intensive Care Nursery suggested that IV therapy could be an important factor in outcome; therefore, the pre-term AGA infants were separated into 2 groups, depending on IV therapy.

Table IV

INTRAVENOUS FLUIDS VERSUS ORAL FEEDINGS

	IV Fluids	Oral Feedings Only
# of infants	15	41
mean time of fluid or oral feeding (hrs.)	3	26
# of children handicapped	1	18
# handicapped, including minimal CNS findings	3	24
# with I.Q. <90	1	13
Mean I.Q.	102	94

Statistical significance of the above data can be seen in Tables V and VI. The data, even on small numbers, are highly suggestive that prompt IV glucose, bicarbonate and fluid therapy are related to a good outcome. The data, at this time, point the direction of further investigations on a controlled basis and not to a firm recommendation that IV glucose therapy be instituted for all pre-term infants. It is not known from these data what IV fluid, per se, accomplishes. It is not known whether the glucose levels were low, nor what IV glucose administration may have done to the levels.

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The cause of the poor outcome of pre-term infants is not known, and it is presumptive to state that spastic diplegia or minimal cerebral dysfunction are due to a lack of glucose in the first hours of life. IV glucose and bicarbonate therapy may alter other metabolic parameters, such as bilirubin, which may be unbound and toxic to the brain, or the glucose may compensate for cold stress.

Furthermore, oral glucose may be just as beneficial as IV glucose if given at the same time. After birth, oral glucose and bicarbonate may need to be given together, orally or by IV.

All of these factors must be investigated before specific therapeutic recommendations are made.

Table V

STATISTICAL SIGNIFICANCE I.Q. BY NURSERY CARE

	Inten. Care	Reg. Care	X ²	P
Total	34	22		
With RDS	15	2	6.18	<.05
IV therapy	15	0	11.10	<.001
I.Q. >90	29	13	3.59	<.10
CNS findings (definite)	9	6	.06	N.S.
Abnormal I.Q. & CNS	10	9	.36	N.S.
Inc. Min. CNS findings	13	14	2.51	<.20

	IV	Oral	X ²	P
Total	15	41		
I.Q. <90 and definite				
CNS findings	1	18	5.23	<.05
Inc. Min. CNS findings	3	24	5.08	<.05

Table VI

STATISTICAL SIGNIFICANCE I.Q. BY NURSERY CARE

	# Pts	Ave. I.Q.	S.E.	
1. 1500-2000 AGA	26	100	2.30	
2. 2000-2500 AGA	30	92	3.42	
3. IV	15	102	2.84	
4. No IV	41	94	2.70	
5. Inten. Care	34	97	2.85	
6. Inten. Care & IV	19	93	4.44	
7. Reg. Nurs.	22	94	3.37	

Comparison	D.F.	Ave. Diff.	S.E.	t	P
1 vs. 2	54	7.89	4.26	1.85	<.10
3 vs. 4	54	8.61	4.80	1.79	<.10
5 vs. 7	54	3.24	4.46	0.73	N.S.
3 vs. 6	32	9.01	5.60	1.61	<.20

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OUTCOME OF TERM SGA INFANTS

In contrast with the pre-term AGA infants, the term SGA infants had relatively little respiratory distress and/or apnea (1 RDS and 2 with apnea out of 36).

Obstetric, labor and delivery complications were related to birth weight (14/15 for the smaller birth weights and 11/21 in larger infants).

Resuscitation was needed in only 3 of 36 infants and IV therapy was necessary for only 1 child.

I.Q. was affected in 10/36 and CNS disorders or minimal cerebral dysfunction was present in 6/36 children.

There was a high incidence of abnormal encephalograms in the SGA groups.

In summary, the initial perinatal course of SGA infants appeared to be relatively uneventful, but their long-term prognosis turned out to be poor. Undetected neonatal hypoglycemia is one possibility for the poor outcome; another could be unrecognized intrauterine infection. Gross or definite congenital anomalies were excluded before the analyses.

Part II

PHYSICAL GROWTH

The later growth in height, weight, and head circumference of pre-term, appropriate-for-gestational-age (AGA) infants versus term, small-for-gestational-age (SGA) infants was examined.

Infants with birth weights between 1500 and 2500 grams were used and their measurements were plotted on standard percentile growth charts (Boston data were used for height and weight, and Denver Child Research Council percentiles used for head circumference).

Table I gives the number of children whose measurements fall into the various percentiles, and Table II, the percentile distribution.

Both groups of children show a shift to the left in height and weight. The pre-term infant's curve for height suggests a bimodal one, but this characteristic is not seen in the curve for weight and head circumference. Head growth is least affected in the pre-term AGA children.

The SGA children's curves are smooth--shifted far to the left--in all 3 physical growth parameters (Figure 1).

The meaning of these data is not clear at this time. Finding that height is more affected than weight and head circumference in pre-term infants is a surprising one and warrants further investigation into the relationship between growth and central nervous system abnormality, or other relationships which have not yet been considered.

It was expected that the SGA children would not be as large as normal children in all parameters and this expectation was documented.

Table I

PHYSICAL GROWTH OF PRE-TERM AGA AND TERM SGA INFANTS
AT APPROXIMATELY 4 YEARS OF AGE

	<3%	3-9%	10-49%	50-90%	>90%	Total # Measured
Pre-term AGA Children with Birth Weights 1500-2000 gms						
Height	8	8	14	15	1	46
Weight	10	7	25	11	0	53
Head Circumference	2	10	20	14	2	48
Term SGA Children with Birth Weights 1500-2000 gms						
Height	9	6	15	4	0	34
Weight	13	5	14	3	1	36
Head Circumference	2	7	10	4	0	23

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Table II

DISTRIBUTION OF CHILDREN IN PERCENTILES OF GROWTH

	<10%	10-49%	50-90%	>90%	Total # Children
Pre-term AGA Children with Birth Weights 1500-2500 gms					
Height	35	30	33	2	46
Weight	32	47	21	0	53
Head					
Circumference	25	42	29	4	48
Term SGA Children with Birth Weights 1500-2500 gms					
Height	44	44	12	0	34
Weight	50	39	8	3	36
Head					
Circumference	39	44	17	0	23

PHYSICAL GROWTH

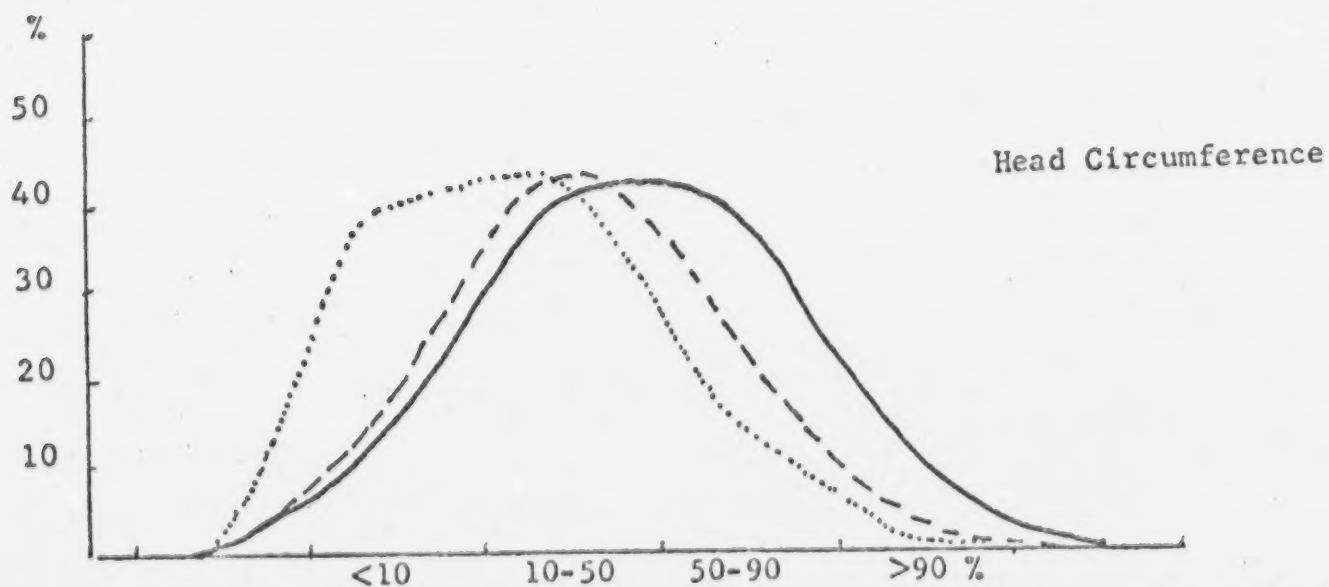
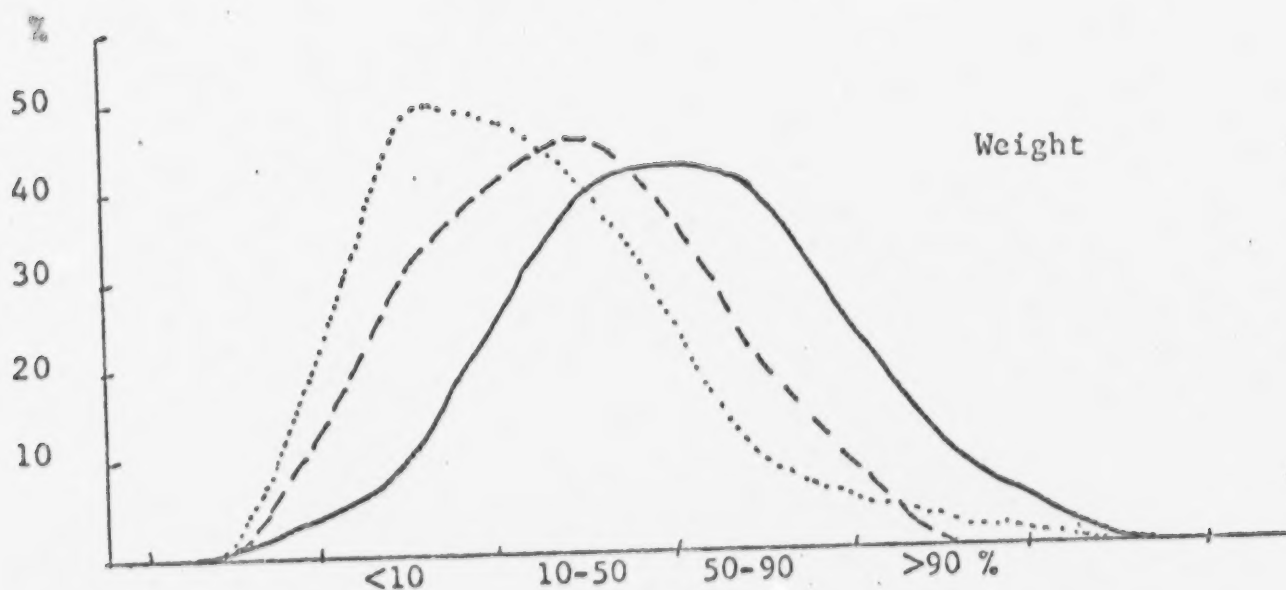
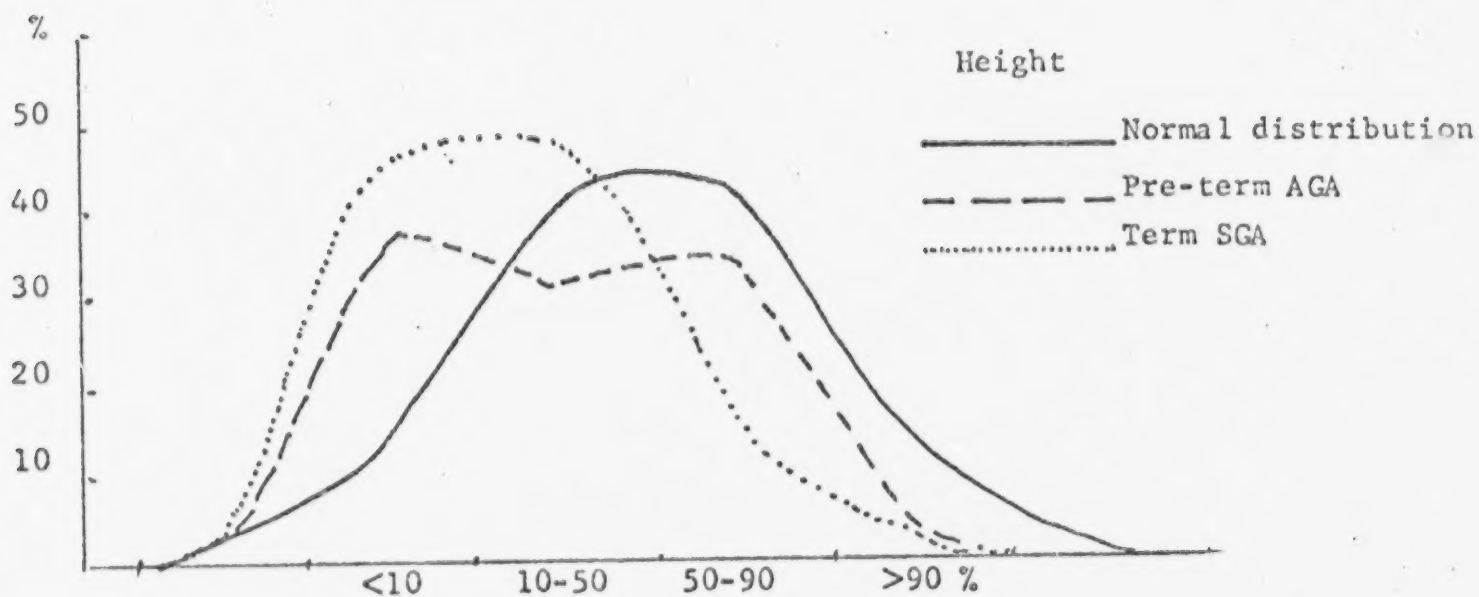


Figure 1. Physical growth at 4 years of age of children who were small for gestational age.

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Part III

CONGENITAL ANOMALIES IN RELATION TO
GESTATIONAL AGE AND BIRTH WEIGHT

In the patients followed, congenital anomalies were present in
3 patients with birth weights <1500 grams
1 AGA infant, 1500-2000 grams
2 AGA infants, 2000-2500 grams
2 SGA infants, 1500-2000 grams
1 SGA infant, 2000-2500 grams

Since congenital anomalies were coded for all admissions during 1963-1965, it was decided to examine the total newborn population for distribution of recognized major anomalies by birth weight-gestational age (Tables I, II, and III).

The very high incidence of congenital defects in infants who die during the neonatal period deserves further investigation.

There is a higher incidence in low-birth-weight infants--11.0% versus 3.2% in infants with birth weights >2500 gms ($p<.001$) and there is a higher incidence in pre-term infants, i.e., 8.9% in infants born before 38 weeks of gestation versus 3.3% in infants of 38 or more weeks of gestation ($p<.001$).

Figure 1 gives the incidence of congenital anomalies by birth weight-gestational age blocks. Although the incidence is higher in low-birth-weight infants in actual numbers of children with anomalies, the largest number of afflicted children occurs in term, appropriate for gestational age (AGA) infants--the group in which the majority of infants are born.

The incidence of congenital anomalies was examined in 4 quadrants, divided by 38 weeks gestation and 2500 grams birth weight (Figure 2). Pre-term low-birth-weight infants had the highest incidence (13.6%) and term low-birth-weight infants the next highest (9.4%); while term infants with birth weights >2500 grams had an incidence of 2.9%.

The incidence of congenital defects by birth weight-gestational age was plotted in graph form (Figure 3), which showed a peaking at 1000-1500 grams and at 28-30 weeks. This block corresponds to the pre-term AGA group by the newborn classification, rather than SGA infants. Further study is needed to clarify the role of intrauterine growth retardation in infants with congenital anomalies.

Table I

INCIDENCE OF MAJOR CONGENITAL ANOMALIES IN LIVEBORN INFANTS
DELIVERED AT THE UNIVERSITY OF COLORADO MEDICAL CENTER 1963-1965

	# Births	# Anomalies	% Incidence
All	3249	140	4.3
Survivors	3169	106	3.3
Neonatal Deaths	80	34	43.0

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Table II

INCIDENCE OF MAJOR CONGENITAL ANOMALIES
BY BIRTH WEIGHT 1963-1965

Weight Group	# Births	# with Anomalies	% with Anomalies
<500 gms	11	1	9.0
501-1000	19	3	15.7
1001-1500	33	12	36.3
1501-2000	85	14	16.4
2001-2500	295	19	6.4
2501-3000	953	29	3.0
3001-3500	1221	43	3.5
3501-4000	512	12	2.3
4001+	118	7	5.9

Table III

INCIDENCE OF MAJOR CONGENITAL ANOMALIES
BY GESTATIONAL AGE 1963-1965

Gestational Age	# Births	# Anomalies	% with Anomalies
<26	15	1	6.6
26-28	8	2	25.0
28-30	13	7	53.8
30-32	23	8	34.7
32-34	55	5	9.0
34-36	19	7	5.8
36-38	316	19	6.0
38-40	914	30	3.2
40-42	1033	31	3.0
42-44	322	14	4.3
44+	35	3	8.5

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Part IV

COMPLICATIONS OF INDWELLING UMBILICAL VEIN CATHETERS

INTRODUCTION

A rare morbidity associated with the use of indwelling umbilical vein (UV) catheters is portal vein thrombosis and subsequent liver cirrhosis (Osaki, *Pediat.* 31:297, 1963). Following this report, the umbilical artery (UA) which had been used to obtain arterial blood samples from infants with the respiratory distress syndrome (RDS) was then used to administer fluids as well. However, when there is difficulty in catheterizing the artery, or when a mechanical pump is not available to regulate the administration of fluids via UA, the UV may be used.

In this hospital, there were over 250 patients from 1960 to 1966 who received intravenous fluids, glucose, and/or sodium bicarbonate via indwelling UV catheters.

There is reason for concern about portal vein thrombosis because of the hypercoagulable state of newborns, which is especially prominent in newborn infants (Markarian et al, *Biol. Neonate* 17:84-97, 1971).

The possibility of introducing infection, using this route of fluid administration, is well-known but this hazard of infection has been weighed against the technical difficulties encountered in administering fluids via small peripheral veins in very high-risk infants.

In a preliminary study of the complications associated with UV catheterization, the feasibility of obtaining information about the liver and spleen using ultrasound scanning of the abdomen was explored. In 15 children, aged 3 to 4 years, examined by ultrasound, 5 of the 15 patients tested had UV catheters inserted for fluid administration during the first few days after birth. Three of the 5 showed evidence of density of the ligamentum venosum or increased connective tissue in this area. Four of the patients with RDS did not receive fluid via UV catheter and one of these children had a questionably abnormal liver scan, while 6 patients without RDS or UV catheters had normal liver scanning.

The examination of abdominal organs by use of the ultrasound technique seemed to offer valuable information and was extended to a high-risk group of children, as described below.

CLINICAL MATERIAL AND METHODS

Mortality and morbidity data from the medical records of all newborn infants cared for in the Newborn and Premature Center at the University of Colorado Medical Center are coded and the data are kept in the Center office. From these records it was found that 86 infants had been treated

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via an indwelling UV catheter during the initial hospital stay. Of these 86, 50 were located and returned for follow-up examinations at approximately 16 months of age. Their ages ranged from 9 months to 2 years.

They received a detailed medical history and physical examination, in addition to ultrasound scanning of the abdomen.

Ultrasound scanning for liver size, as well as for evidence of scarring or abnormal liver parenchyma, was carried out (Holmes, J. H., Diagnostic Ultrasound: Proceedings of the First International Conference, Plenum Press:249, 1966).

The pictures obtained from the procedure were studied for organ size and character of organ parenchyma.

The distance the liver edge extended below the right costal margin was recorded and the surface area was calculated (by means of a planimeter) from the scan at 1 centimeter (cm) above the right costal margin.

RESULTS

Complete data were obtained on 47 infants. The results in relation to duration of the indwelling catheters are listed in Table I. The liver surface is shown in square cms and the distance the liver extended below the right costal margin is given in cms.

Only a slight relationship exists between the two measurements because of the varied shape and thickness of the liver. The smallest surface area occurred in a liver which did not extend below the right costal margin and the largest surface area was present in a liver which extended 4 cms below the right costal margin, but the overlap in surface area and distance below the right costal margin was so great as to render the relationship insignificant.

If one considers a liver which is 3 cms or more below the costal margin readily palpable, then the incidence of clinically enlarged livers in this population is 19 out of 39 scans, or 48%. There was reasonably close agreement between the clinical estimate of liver size and the measured distance by ultrasound in the patients presented herein.

The surface area of the liver was plotted against body weight (Figure 1). There is a trend which shows an increase in liver size as body weight increases, but the range of liver size at any weight is great. It is of interest, however, that the largest area in relation to body weight and the smallest area in relation to body weight occurred in children who had UV catheters in situ for 5 days or more.

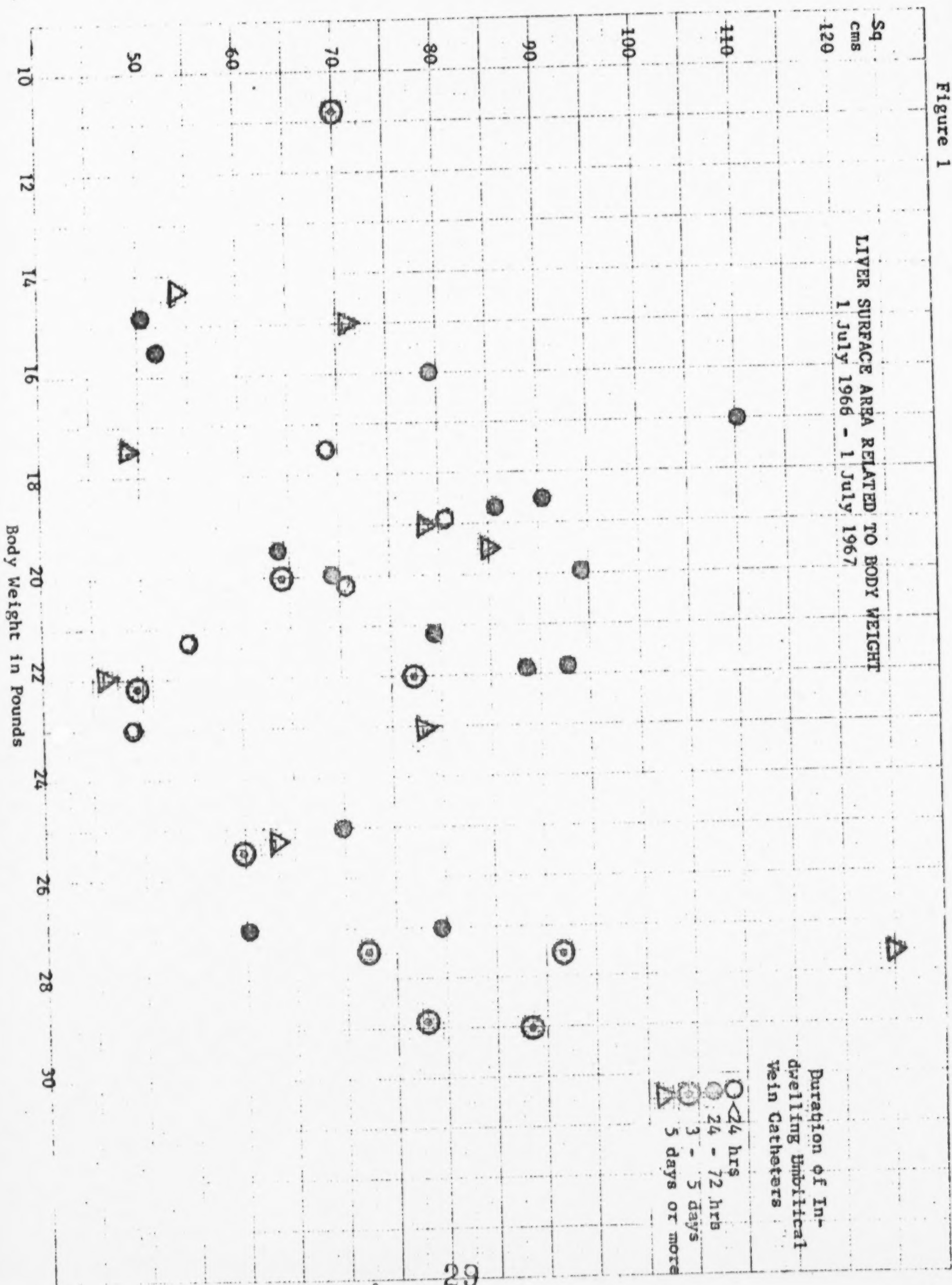
Selection of so young a population was unfortunate because the inability of these patients to cooperate and the procedure added to the technical difficulties in obtaining clear pictures and resulted in very little information regarding the condition of the liver parenchyma, including fibrosis, in the vicinity of the ligamentum venosum.

Table I

DURATION OF INDWELLING UMBILICAL VEIN CATHETERS
AND LIVER SIZE
1 July 1966 - 1 July 1967

24 hr or less				Duration of Catheter				5 days or more			
Pt's Name	Liver Surface (sq cms)	Below RCM (cms)	Pt's Name	Liver Surface (sq cms)	Below RCM (cms)	Pt's Name	Liver Surface (sq cms)	Below RCM (cms)	Pt's Name	Liver Surface (sq cms)	Below RCM (cms)
Tolles	49	2	Schmidt	64	3	Owens	49	1	Laes	48	2
Dukes	70	4	Van Vleet	90	3	Velasquez	72	2	Osaki	54	1
Gabriel	54	4	Hoerauf	52	3	Condon	89	3	Wells	63	4
Addington	68	2	Ward	70	2	Hurley	92	3	Reyes	85	3
Rohe	81	3	Schlidt	60	0	Green, Andrew	78	1	Peter	71	3
			Darling	79	4	Wilson	70	3	Kitzmire	125	4
			Gneiser	85	3	Colby	60	0	Green, Amy	46	2
			Baca	110	2	Sears	64	3	Love	78	2
			Silcott	87	1	Ramirez	77	2	Donnelly	40	0
			Ellsworth	79	4				Gerton	77	1
			Brown	50	0						
			Naugle	94	3						
			Diamond	92	6						
			Biggs	42	0						
			Cardwell	79	1						

Figure 1



DISCUSSION

The frequency with which the umbilical vein is used as an avenue for an indwelling catheter gives concern about the possible complications of this route of fluid administration.

Immediate complications include infection, perforation and liver damage, while later results include the rare occurrence of portal vein thrombosis.

Because of the proximity of the portal vein, a UV catheter may sometimes be threaded into the portal vein instead of into the inferior vena cava (Figure 2). The presence of the catheter in the umbilical vein may slow the flow of blood from the portal vein. This relative stasis of blood in a patient with hypercoagulability sets the stage for intravascular coagulation.

Exchange transfusions are routinely carried out via the umbilical vein, but this procedure is of short duration and the catheter is rarely left in the vein for long periods of time. However, portal vein thrombosis can occur under these circumstances since the first reports of cirrhosis of the liver were in patients who had repeated and/or traumatic UV catheterization for exchange transfusion.

Generalized infection is so frequent in high-risk newborns that a causal relationship between UV catheterization and sepsis is difficult to document. Redness and induration of the umbilical stump, following UV catheterization, also is common and not necessarily associated with generalized infection. However, a very high incidence of positive cultures from the tip of umbilical catheters has been found on removal of the catheters.

Jaundice, also, is so frequent in the newborns who will be treated via UV catheters, i.e., infants with Rh iso-immunization and RDS, that traumatic or septic liver damage is nearly impossible to document.

The need for a tool to help differentiate these problems is apparent, and it was because of this need that information from ultrasound scanning of the liver was investigated.

Abdominal ultrasound scanning resulted in good pictures in older children and it was possible to examine definitive structures in the parenchyma. The results in infants and toddlers were variable. Only a few clear pictures were obtained, out of the 47 examined. Even so, liver shape and size could be determined.

Because of the wide variation in shape and thickness of the liver, large differences must be demonstrated before an abnormal state can be defined on the basis of size alone.

In the cases presented herein, the frequency of finding the liver 3-4 cms below the costal margin was impressive, even though parenchymal pathology was not demonstrated. Only one case was of concern from a clinical standpoint.

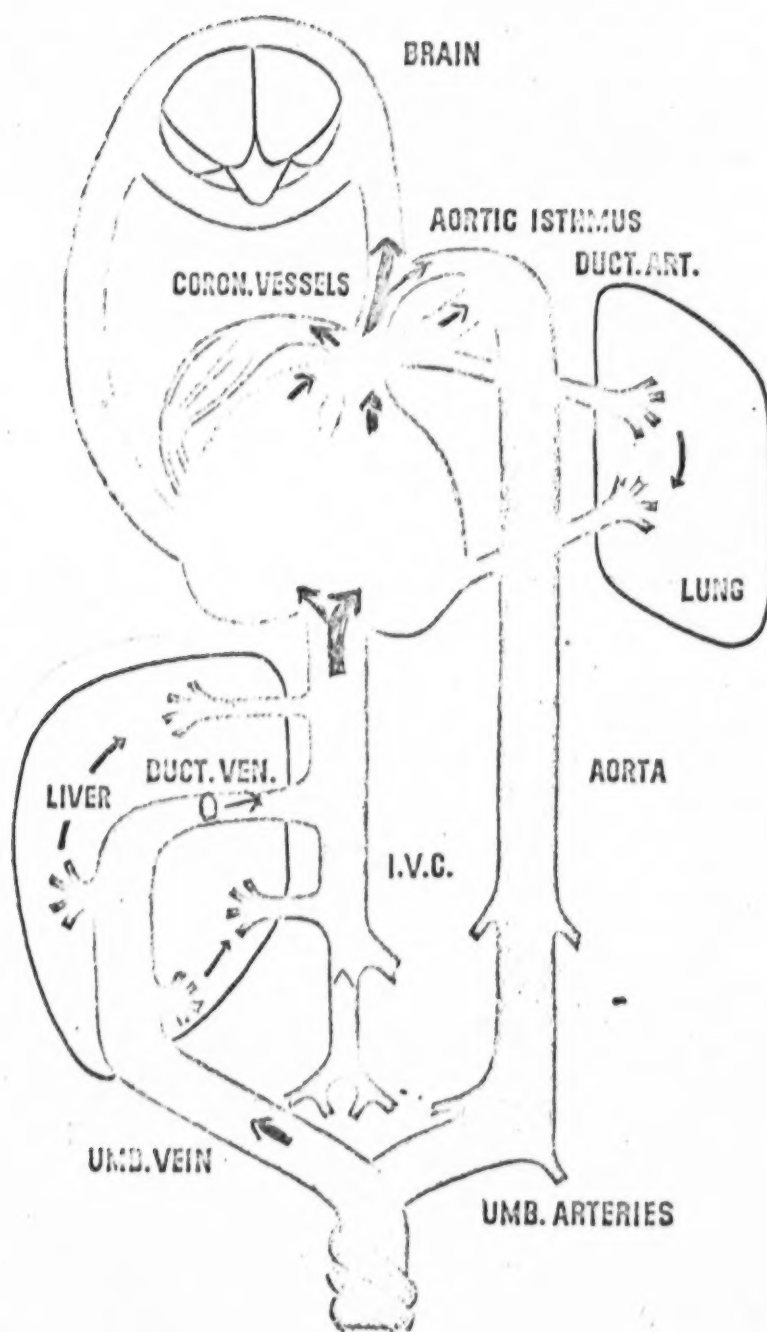


Fig. 2: The Circulation in the Foetus

From: Human Foetal and Neonatal Circulation,
Lind, Stern and Weglius, C. C. Thomas,
Springfield, Illinois, 1964

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SUMMARY

Ultrasound screening for liver pathology was carried out in 47 infants and toddlers who had received fluids in the neonatal period via an indwelling UV catheter and in 15, 3- to 4-year-olds, who were high-risk infants.

The pictures from the older children were distinct enough to detect density in the area of the ligamentum venosum in 4 of the patients. Three of these had been treated in the neonatal period via UV catheters and the other child had RDS.

Pictures from the younger children were less distinct, but an impressive incidence of hepatomegaly was noted--48% of the infants had liver edges 3 or more cms below the right costal margin and 7 were 4 to 6 cms below the right costal margin.

CONCLUSIONS

Ultrasound screening of the liver is a useful additional tool to investigate the condition of this organ. The older the children, the better the success in visualizing the parenchyma but even in small infants, liver size and shape can be determined.

Dev. Med. & Child Neurology

Part V

Studies on Head Shape and Size of Normal Newborn Infants;

Part I Their Relationship to Gestational Age and Birth Weight

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Head circumference and biparietal diameter have been shown to correlate well with birth weight and gestational age (Lubchenco, et al. 1966, Thompson, et al. 1965). The present study considers other measurements of head shape and size in the newborn infant to determine whether they interrelate mathematically, whether the inclusion of more than one measurement of head size provides improved correlations with birth weight and gestational age, and to establish normal values for comparison with growing premature infants (Baum and Searls, 1970).

MATERIALS AND METHODS

Measurements were made on a total of 77 normal newborn infants born at the University of Colorado Medical Center. In accordance with the Colorado classification of newborn infants (Battaglia and Lubchenco, 1967) based on birth weight, gestational age and adequacy of intrauterine growth. There were 55 who were appropriate for gestational age (AGA), 8 who were large for gestational age (LGA) and 14 who were small for gestational age (SGA). Infants were included in the study only if their estimated gestational age by physical examination agreed with that calculated from the dates of mothers' last menstrual period.

All measurements were made by one observer (J.D.B.). A pilot survey had shown head moulding to be largely resolved

2-Studies on Head Shape and Size in Normal Newborn Infants-Baum and Searls within 36 hours after birth. Measurements were made, therefore, between 36 hours and 7 days of age. Occipitofrontal circumference (OFC) was measured with a disposable paper tape. Head shape was recorded with a flexible plastic stick which was closely applied to the head in the same plane as that of head circumference measurement. It was then removed and the shape enclosed traced onto paper. From the tracing, direct readings of anteroposterior (AP) and biparietal (BP) diameters were taken, and the area enclosed measured by planimeter. This represented the cross-sectional area (A) of the head in the plane of the measured OFC (Figure 1).

RESULTS

Table 1 shows the mean, range and standard deviation for gestational ages, birth weights and head measurements in the infants studied.

Table 2 shows the correlation coefficients for the various measurements of head size with gestational age and birth weight. For the AGA infants all measurements of head size were closely related to both gestational age and birth weight. The best correlation was between the product of the AP and BP diameters and birth weight ($r = .931$). For SGA infants the correlations were not as close; the association was better between head size and birth weight, than between head size and gestational age; the best correlation was again between the product of AP and BP diameters and birth weight ($r = .869$). There was

Gestational ages, birth weights and head measurements on 77 newborn infants.

Table 1

	55 Infants AGA			8 Infants IGA			13 Infants SGA		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Gestational Age (weeks)	37	3.6	28 to 43	39.75	1.75	37 to 43	36.79	2.04	32 to 41
Birth Weight (grams)	2456	739.6	990 to 3640	3831	171	3570 to 4000	1754	378	1180 to 2570
Head Circumference (cms)	32.26	2.86	24.2 to 37	35.44	1.18	34 to 38	29.53	1.7	26.5 to 31.75
BP Diameter (cms)	8.59	0.88	6.3 to 16.0	9.81	.35	9.1 to 10.3	7.81	.48	6.9 to 8.6
AP Diameter (cms)	11.3	0.97	8.7 to 13.3	12.3	.66	11.4 to 13.5	10.41	.61	9.3 to 11.3
Cross-Sectional Area (cms ²)	78.09	13.3	43.4 to 100.4	95.06	6.36	88.8 to 109	64.7	7.45	50.4 to 77

Table 2
Correlation coefficients between head measurements and
gestational age and birth weight, for the infants
studied. ACA, SCA and LGA infants are considered separately.

	ACA Infants		LGA Infants		SCA Infants	
	Gestational Age	Birth Weight	Gestational Age	Birth Weight	Gestational Age	Birth Weight
Head Circumference (cms)	.920	.914	.199	.351	.769	.860
BP Diameter (cms)	.911	.913	.638	.093	.694	.773
AP Diameter (cms)	.902	.889	.000	.358	.796	.819
Area (cms ²)	.925	.927	.276	.271	.779	.879
AP x BP	.928	.931	.311	.315	.802	.869

3-Studies on Head Shape and Size in Normal Newborn Infants-Baum and Searls
no association between head size and birth weight or gestational
age in the LGA infants.

The number of SGA (13) and LGA (8) infants was small to study
the ways in which their heads differed from the AGA infants in
their relationship to gestational age and birth weight. However,
from the correlation coefficients (Table 2) it is clear that it
was not simply a matter of head size being appropriate for maturity,
as opposed to birth weights.

Pooling all the data from SGA, LGA, and AGA infants, close
relationships could be shown to exist between head size and
birth weight or gestational age. The best relationship was
between the product of the diameters AP and BP and birth weight
(Figure 2). From these data, given the product of the AP and
BP diameters, one could predict the birth weight: 1 SD = 288.9 grams.

There was a close interrelationship between the various para-
meters of head size for all infants.

$$\begin{array}{ll} A = .8 (BP \times AP) & r = .997 \\ OFC = 3.66 \quad A & r = .990 \\ OFC = 1.62 (BP + AP) & r = .991 \end{array}$$

This is a reflection of the consistency of head shape within
this group of newborn infants.

DISCUSSION

In the newborn, measurements of OFC are used as an index
of brain growth, and as a simple screening test for abnormal

4-Studies on Head Shape and Size in Normal Newborn Infants-Baum and Searls deviation in head size. It has also been shown that of all neonatal physical measurements, OFC (presumably reflecting brain growth) is least modified by intrauterine undernutrition (Lubchenco, et al. 1968).

In the present study, close correlations were established between head size as measured by OFC, AP and BP diameters and cross-sectional area and gestational age and birth weight for AGA and SGA infants. No such relationships held for the 8 LGA infants.

The association between head size and birth weight has found application in the prenatal prediction of fetal weight. Many studies have shown prediction of fetal weight with varying degrees of accuracy, using the biparietal diameter as measured by ultrasound (Thompson, et al. 1965, Goldberg, et al. 1966, Kohorn 1967, Hibbard and Anderson 1967, Willocks, et al. 1967). In the present study, the best relationship derived from head size with birth weight was that using the product of the AP and BP diameters. Due to the minor variations in head shape, use of the biparietal diameter alone might be expected to correlate less well with birth weight than some factor including a measurement of the anteroposterior diameter. It would seem that inclusion of an ultrasonic measurement of the AP diameter would improve the accuracy of fetal weight prediction.

After birth, infants are occasionally seen with head shapes outside the normal variations; e.g., infants with craniosynostosis (Shillito and Matson 1968) and some ex-premature

5-Studies on Head Shape and Size in Normal Newborn Infants-Baum and Searls infants (Baum and Searls 1970). In these cases, measurements of OFC may lead to misleading high values for head size, since an area has its smallest perimeter when it is a circle and the more it is deformed from that shape, the greater its perimeter will become. From the present study on heads of normal shape, a formula was established interrelating OFC, AP and BP diameters and A. When considering the size of a head of unusual shape, calculations from measurements of AP and BP diameters or from A, will give the circumference of that cross-sectional area were it of normal configuration.

SUMMARY

Studies were made of head size and shape in newborn infants. Good correlations were established between head size and both gestational age and birth weight in infants other than those large for their gestational age.

Pooling all the data, the best correlation existed between the product of the anteroposterior (AP) and biparietal (BP) diameters and birth weight.

Formulae were derived for calculating head circumference from measurements of AP and BP and cross-sectional area of the head; in this way spuriously large measurement of head circumference in unusually shaped heads might be corrected for skull deformity.

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Donald Searls

Part V

Studies on Head Shape and Size of Premature and Ex-Premature Infants

Part II

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Occipitofrontal head circumference (OFC) is an established useful index of brain size and growth. There is remarkable consistency of head circumference at various ages in different races; this lends reliability to the use of a single measurement and its comparison with published data (Wellhaus 1968). However, any major deviation from the normal configuration of the skull may lead to misleadingly high values for OFC since an area has its smallest circumference when it is a circle; the greater it is deformed from that shape the greater will be its perimeter.

It is common experience that pre-term and low birth weight infants have flattening of their skulls as they lie with their heads to the side. It is questionable for how long these deformities persist. In the present study head circumference, shape and cross-sectional area have been measured in pre-term, low birth weight infants and in a group of young adult ex-premature patients. From these measurements the dynamics of head growth in these patients have been studied.

MATERIALS AND METHODS

All measurements were made by one observer (J.D.B.), using the methods described for normal infants (Baum and Searls, 1970).

Newborn Studies:

Pre-term, low birth weight infants from the newborn intensive care unit at the University of Colorado Medical Center were studied at weekly intervals. Control measurements for head shape were obtained from a group of 55 infants of appropriate weight for

2-Studies on Head Shape and Sizes in Premature and Ex-Premature Infants
their gestational age (Baum and Searls, 1970) with gestational
ages ranging from 28-44 weeks, while postnatal ages varied be-
tween 36 hours and 7 days. Preliminary studies of skull moulding
indicated that skull deformation had resolved, for the most part,
within 36 hours.

One ex-premature infant of 17 months was also studied.

Ex-Premature Adults:

Forty-five young adults born at the University of Colorado
Medical Center between 1950 and 1953, with birth weights of 1500
grams or less were also examined.

RESULTS

Pre-term, low birth weight infants: Fourteen pre-term low
birth weight infants were followed longitudinally with serial
measurements of head shape and OFC (Table 1). In each case
the serial skull tracings showed a pattern of progressive
flattening (Figure 1).

Using the ratio of the diameters AP to BP as an index of
head shape, the degree and progression of skull deformation
was studied (Figure 2). Within the postnatal period up to
60 days (which included all measurements from 13 of the
14 infants) the best fit for the data was a straight line (X)
with a correlation coefficient of .74. When the points were
added from the infant who was followed up to 99 days, the
regression line became curvilinear (Y) with correlation
coefficient of .72. Three of the pre-term infants were small

Table 1

14 Pre-term, Low Birth Weight Infants

	Range	Mean
Birth Weight (grams)	850 - 2120	1590
Gestational Age (weeks)	28 - 36	32.5
Head Circumference (cms)	24.5 - 31.5	28.2
Number of Readings	3 - 10	4
Duration of Follow-Up (days)	16 - 99	31

in weight for their gestational age; they showed the same pattern of head flattening as the group as a whole.

From the data on normal newborn infants it has been shown that the cross-sectional area (A) is related to the OFC by the formula: $OFC = 3.66 \sqrt{A}$ (Sawm and Searls, 1970). Applying this formula in two cases where flattening of the head was extreme, the head circumference was calculated as though the skull were of normal shape. In this way spuriously high results for OFC were corrected for head shape. Figure 3 shows the progression of the measured OFC for these two infants, which crossed from below the 10th percentile to the 50th percentile; the same heads are also shown with the OFC's derived from their cross-sectional areas by the formula for normal shaped heads. The effect of head flattening on OFC is illustrated (Figure 3).

The effect of flattening for one ex-premature infant of 17 months (birth weight 980 grams; gestational age 28 weeks) is shown in Figure 4. In this case the large head circumference was accounted for by skull deformation. There were no other features to support a diagnosis of hydrocephalus.

Young Adult Ex-Premature Patients:

Forty-five ex-premature infants were studied (Table 2), and compared with normal data (percentile grouping) for Colorado young adults (Child Research Council 1970). AP diameters were significantly greater ($\chi^2 = 11.7$; $P < .05$); and BP diameters were significantly smaller ($\chi^2 = 51.5$; $P < .001$);

Table 2

45 Ex-Premature Young Adults

	Range	Mean	S.D.
Birth Weight (grams)	709 - 1500	1170.6	171.9
Gestational Age (weeks)	26 - 39	30	2.5
Age at Follow-Up (years)	16 5/12-20 - 5/12	18 1/2	9/12
Head circumference (cms)	51 - 57.5	54.4	1.9

4-Studies on Head Shape and Sizes in Premature and Ex-Premature Infants and OFC's were significantly smaller ($\chi^2 = 14.35$; $P < .003$). Skull deformity of low birth weight infants thus persisted into adult life (Figure 5). The mean AP:BP ratio for this group of patients was 1.33; there are no normal data on AP:BP ratios in adults for comparison.

DISCUSSION

Small pre-term infants generally lie with their heads turned laterally. The head position is due to the relatively large head mass and poor neck muscle tone. Moreover, the skull bones of premature infants are thin and soft. The head of the fetus is supported in utero by the liquor amnii and develops with a near circular cross-sectional shape; after birth, the head of the infant born before term deforms under its own weight.

Intrauterine growth charts for head circumference are derived from cross-sectional data on newly-born infants at various gestational ages (Lubchenco, et al. 1966). Justesen (1962) observed that when a premature child had reached the weight of a term newborn, its head circumference was slightly greater than that of the mature infant. The explanation for this may be the elliptical postnatal head growth of the small pre-term infant, with the production of a relatively large perimeter for the cross-sectional area of the head.

In the present study, 3 infants were included who were small in weight for their gestational ages (SGA), according to the Colorado Intrauterine Growth Chart (Lubchenco, et al. 1966).

5-Studies on Head Shape and Sizes in Premature and Ex-Premature Infants

These infants showed the same pattern of skull deformation as the other pre-term infants. SGA infants are by definition more mature than other infants of similar birth weight; their skull bones are usually thicker and harder and, presumably, less liable to postnatal deformation. However, the present cases were pre-term in addition to being SGA.

Serial measurements of head flattening, as measured by the ratio of the diameters AP:BP, showed this to be a progressive phenomenon up to about 60 days after birth. The infant followed beyond 60 days showed a tendency for the moulding to regress. With improvement in the neck muscle tone and a hardening of the skull bones, one would expect at least an arrest in the progression of head deformation. The mean AP:BP ratio for the adult ex-premature infant was 1.33. There is no normal data on the ratio for comparison, but clearly at some time between the early infancy and adulthood, much of the moulding resolves. The ex-premature adults did, however, show a persistence of the skull deformation acquired neonatally. Compared with normal data for young adults, the ex-premature patients had significantly narrower skulls. In addition the heads were significantly elongated despite the fact that the OFC's were smaller than normal. This further illustrates the marked degree of persistent moulding in these ex-premature patients. The small head size of these patients will be further considered as part of an 18-year follow-up of their overall growth (Lubchenco and Baum, 1970).

6-Studies on Head Shape and Sizes in Premature and Ex-Premature Infants

SUMMARY

Studies on skull deformation in low birth weight infants are reported. These heads flattened significantly in the neonatal period as a result of head posture. Ex-premature adults had smaller heads with a persistence of the skull deformation acquired neonatally.

It is suggested that the skull shape be taken into account in the interpretation of head circumference measurements in growing and ex-premature patients.

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